Critical Care Management of COVID-19 Patients

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Mechanical Ventilation (Drayton)

What is your general PAD pharmacotherapy strategy in the ICU pre-COVID-19?

- Ultimate goal is light sedation
- IV push fentanyl post-intubation
  - Use IV pushes as long as possible, switch to fentanyl infusion if multiple boluses needed
- If a fentanyl infusion is administered, consider adjunctive sedative agent with either propofol or dexmedetomidine
- Utilize a nurse-driven sedation protocol in the ICU
  - Low dose IV push BZD for agitation for vent dyssynchrony, limited to 5mg/day to try and reduce risk of delirium
- Avoid BZD infusion unless deep sedation +/- NMBA infusion is required

How has your PAD strategy changed with the COVID-19 pandemic? If there weren’t any drug shortages would you be doing anything different?

- The PAD strategy hasn’t drastically changed, keep the principles from above in mind for COVID-19 patients
- Have had to dig into the “toolbox” to find alternative agents to use
- Make sure the RN, RT, Providers, and everyone on the team knows the plan, because it isn’t business as usual
- Still try to use the lowest amount of sedation, but avoid undersedation which can lead to patients becoming dyssynchronous with the vent
  - These patients require deeper levels of sedation than normal
  - Look to balance the need for deep sedation, while still using the lowest amount the patients can tolerate
- Attempting to spread out the use of sedatives and analgesics to get the most utility in the greatest number of patients
An example of a common multi-modal PAD regimen:
- Fentanyl infusion (or other opioid due to drug shortages) + IV push boluses PRN
- Propofol +/- dexmedetomidine infusion
- Lorazepam IV push bolus PRN
  - Individualized doses to use the lowest possible
  - A big change is using lower infusion rates of multiple sedatives to achieve sedation goals

Many first-line PAD agents are going to be or are already on shortage. Have you developed any initiatives to try and conserve these medications?
- Using propofol and dexmedetomidine simultaneously at lower doses rather than monotherapy at a higher dose
  - Higher risk of hemodynamic instability with concomitant use from SPICE III and other single-center research studies
    - Work to minimize ADE by using lower doses of both
- Patients’ triglyceride (TG) levels rise quickly because of the sHLH type syndrome occurring in COVID-19 patients
  - Add low dose dexmedetomidine to reduce their propofol dose
  - Low dose PRN IV push BZD for breakthrough agitation

Due to a fentanyl shortage, developed a plan of utilizing various IV opioids for pain management
- Fentanyl for patients with ESRD on renal replacement therapy
- Hydromorphone for patients with tenuous renal function or AKI
- Morphine in patients with normal renal function
  - Re-evaluate throughout the day with the ICU team
- Want to try and maintain stock for high-risk patients while attempting to maintain safe and effective pain management
  - IT team assisted with building lists to assist with medication management and ease safety concerns
Are you using any other strategies beyond opioid rationing or rotating to help conserve medications?

- Used alternative opioids such as enteral oxycodone and hydromorphone infusions when fentanyl infusions were on shortage
  - With the high dosage of opioids these patients were requiring, the risk of oxycodone accumulating in patients with poor renal function is high
- Haven’t transitioned to fentanyl patches due to the issues with absorption due to the high fevers COVID-19 patients experience
- Avoiding gabapentin due to concomitant renal impairment
- Will use adjuvant agents such as acetaminophen and things that don’t accumulate in renal failure
- Haven’t had to use the fentanyl analogues (for example sufentanil and remifentanil) but do have a remifentanil order set ready to use if necessary

How are you attempting to manage your propofol supply?

- Initially allowed propofol tubing to be exchanged every 24 hours rather than every 12 hours for conservation purposes
  - Changed back to every 12 hours for safety concerns
  - The package insert data is based on multi-use vials or syringes and not the way we are currently using it (e.g. longer dwell time in the tubing)
  - The manufacturers of propofol don’t have the data or won’t share it, even after reaching out to the company
    - But with a pandemic, in certain situations, we may have to assume some risk
- Avoid propofol in RSI for conservation and due to the risk of hypotension
- Use 20 mL propofol vials to prime tubing when it’s time to exchange
Example on how to prime via @KAckerB_PharmD (Kim Ackerbauer)

When should we switch from propofol due to hypertriglyceridemia? What is your personal practice and is there literature to support?

- Drayton is more liberal than others and uses a cut-off of 1000 mg/dL
  - Based this on data from John Devlin’s 2005 Pharmacotherapy article
    - They found very few cases of pancreatitis developing even with average triglycerides in the 600-700 mg/dL range
  - ASPEN guidelines have a triglyceride cut-off of 1000 mg/dL in regard to the use of IV lipids
- Triglycerides are being checked every 24-48 hours routinely

Have you encountered PRIS or expect to see this in COVID-19 patients any more than other critically ill patients?

- The general risk based on published data is 1 case of PRIS for every 1500-5000 patients
Don’t think we know enough about COVID-19 to say they’re at higher risk of PRIS
  o Frequent monitoring will help catch it early if it occurs

Are you using ketamine more for COVID-19 patients than you would have otherwise used?

  ▪ It was used in many patients before, but not a first-line or routinely used agent for sedation
    o Use has increased to help achieve a moderate level of sedation to avoid the use of BZD infusions
    o When propofol is unavailable or unable to be used, commonly switch to dexmedetomidine and ketamine infusions
  ▪ Monitoring for viral cardiomyopathy or dysautonomia
    o Being careful and vigilant with its use
  ▪ Has also found a risk of drug fever with the use of ketamine

Are you seeing hypersalivation/hypersecretions from the use of ketamine? Are you pre-treating to help prevent this?

  ▪ Not avoiding its use due to this ADE
  ▪ Also not pre-treating to dry the secretions up
    o These patients are at risk of VAP and don’t want to dry up those secretions and increase their risk of pneumonia
  ▪ Haven’t had to switch from ketamine, but will switch prior to extubation if there are excess secretions

Another concern is the fluid overload from using ketamine, with the emphasis on achieving neutral or negative fluid balance in COVID-19 patients. Have you made any changes to help prevent this?

  ▪ First used the 2 mg/mL concentration and found early that this would not work due to the amount of fluid these patients would receive just from ketamine
Used 10 mg/mL ketamine concentration in status epilepticus patients, and now use this in COVID-19 patients
  - Still gets more fluid than we’d like, but it’s an improvement

What has been your general practice regarding the use of neuromuscular blockers in COVID-19 patients? Has your practice changed in an attempt to preserve them?

- Even pre-COVID-19, NMBA infusions weren’t as common as in other institutions
- Created an initiative to use PRN IV push cisatracurium 15-20 mg IV q2hr in those patients who are deeply sedated
  - Ensure the team is aware when the drug was given to assess clinically if it was effective
  - If the patient desaturates again, will likely repeat the PRN dose
    - Small patients may receive a lower 10 mg dose
- Far fewer patients are receiving NMBA now compared to the beginning of the COVID-19 pandemic
- When using an infusion, titrate the NMBA infusion based on ventilator compliance rather than train-of-four

Have you implemented anything to help preserve PPE?

- Moving pumps outside of the room
  - Keeping in mind it takes 2-5 minutes for rate changes to reach the patient
  - May move pumps back in for a code blue or pre-code situation
    - Some risk of overshooting our target due to the longer time to effect
    - Titrate every 3-5 minutes compared to every minute with the pump changes
Have you started limiting the use of inhaled bronchodilators for COVID-19 patients?

- Avoiding nebs in these patients due to the risk of the ventilator circuit malfunctioning
- Switched to MDI as an alternative
- However, the bronchodilators haven’t been very effective
  - Switched to using only in patients with an indication such as asthma or COPD

These patients may develop microthrombi in their lungs, are you looking into using an inhaled anticoagulant?

- Looking into it, but there’s very little data to support, and haven’t started doing this yet

Have you had any success with using inhaled pulmonary vasodilators such as epoprostenol or nitric oxide for hypoxia?

- Not using as a standard of care
  - Some data to support inhaled nitric oxide in MERS (although COVID-19 is a different disease state)
- In patients who are compliant with the ventilator but have a high P:F ratio, may use inhaled epoprostenol
  - Have seen a positive effect in more than half of them
  - Looking internally to see who should receive it
    - Might make number look better without changes in outcomes
- May help reduce oxygen toxicity or allow the use of lower PEEP values
Any advice for Pharmacists or healthcare providers who are caring for critically ill COVID-19 patients?

- It’s a marathon, not a sprint
  - Focus energy on positive multidisciplinary collaboration
  - Be sure to preserve yourself and your colleagues/friends/family
  - Prevent burnout if you can
- Sharing resources
- Being active in professional organizations and on social media
  - Able to build relationships
  - Run ideas past peers and colleagues to learn from each other
- Try to participate in research, whether its RCT or observational studies
  - Contribute to the literature to help answer treatment questions

Cardiovascular Care (Peter)

What vasopressor are you using as first-line treatment for patients who are hypotensive?

- Depends on the etiology of their shock
- In septic shock, still following the SSC vasopressor algorithm
- If hypotensive due to sedation, using more phenylephrine to preserve stock of norepinephrine

Have there been any changes to vasopressor compounding and utilization with the COVID-19 pandemic?

- Changes have occurred not only for vasopressors, but other medications as well
- To help reduce waste:
  - Using drug stability data, extended length of administration time for specific critical care medications
    - Up to 96 hours at room temperature
    - Some for 10 days if refrigerated
  - Have also used higher concentrations to reduce the number of bags needed and extending the time infusions can be used
Are smart pumps being placed outside of patient rooms?
- It’s not being done in every patient, but in certain patients they are
- Some considerations to keep in mind:
  - Clean them appropriately when moving from inside to outside the room
  - Ensure tubing is secured, un-kinked, and off the floor
  - Priming tubing adequately
  - Also worried about occlusion alarm which may not work as effectively or delay the alert
  - May see a delayed response or over-shooting your intended target

Plans for hypotension management if first-line vasopressors go on shortage?
- Working to preserve vasopressors based on compounding/stability changes [discussed more above]
- May increase use of oral midodrine, but many patients haven’t had prolonged periods of hypotension
- Hesitant to use push-dose vasopressors due to medication safety concerns:
  - Many may be unfamiliar with push-dose vasopressor administration leading to undertreatment or overshooting our blood pressure target

What is your anticoagulation strategy in these high-risk COVID-19 patients?
- It’s been changing weekly based on new information being published
- Some studies have shown high rates of VTE (25-40%)
  - But these studies include little to no information on VTE prophylaxis
  - Hard to say what the true VTE rate is in this patient population
- Information that might increase your suspicion/concern for a clot developing:
  - Elevated D-dimer levels
  - Typical signs/symptoms (swelling, redness, pain) indicating a possible VTE event
  - If acutely hypoxic disproportionate to respiratory/radiographic findings
  - Unexplainable RV dysfunction on Echocardiogram
- If any above are present, should be more suspicious

- Hematology colleagues developed institutional guidelines (not policy/protocol)
- Preferentially using enoxaparin (for both prophylaxis and treatment) to reduce amount of times the RN enters the room
- Recommend higher than normal VTE prophylaxis in patients you may have a higher suspicion or concern for an event
  - D-dimer > 2-3x ULN + other s/sx VTE
- VTE prophylaxis in these patients (with normal renal function)
  - 0.5 mg/kg enoxaparin subQ Q12hr
- VTE prophylaxis with concomitant renal dysfunction
  - 30 mg enoxaparin subQ Q24hr
  - 7500 units UFH subQ Q8hr
- Utilize anti-Xa monitoring: Level drawn 4 hours after the 3rd dose
  - Goal range: 0.4 – 0.6

**Are the anti-Xa levels being altered (falsely increasing or decreasing) by the COVID-19 disease?**
- For the most part, the levels have seemed valid
  - Some instances where aPTT and anti-Xa levels aren’t correlating leading to issues with interpretation

**How is anticoagulation being addressed for patients receiving CRRT/ECMO?**
- Anecdotal issues with circuit clotting more frequently for CRRT patients
  - Running UFH through CRRT circuit initially
  - If clots persist, will use systemic UFH full-dose anticoagulation
    - May also switch to argatroban infusions instead of full-dose UFH
- ECMO patients are already at a higher risk for VTE events
  - Most should continue following their ECMO anticoagulation protocol/guideline

**In the face of a potential shortage, are you considering any alternative anticoagulation strategies?**
- Not currently looking at adding other anticoagulants to the formulary
- DOAC in some situations may be appropriate
  - Don’t expect procedures and patients have adequate renal function
- In critically ill patients, continue using parenteral anticoagulants
  - Switch to DOAC once the level of care has been downgraded
The use of thrombolytics for ACS has increased to help preserve PPE and reduce the potential exposure to staff. Is this something you’ve started implementing as well?

- Interventional cardiologists have been working on an ACS guideline in COVID-19 positive patients
- Important consideration because many COVID-19 patients can have myocardial injury, especially severe cases
  - Elevated troponin levels and/or EKG changes
- In some STEMI patients, it may be reasonable to use thrombolytics if you’re unable to perform PCI in a safe manner
  - Tenecteplase is the thrombolytic of choice for management in ACS
- Education on this possible change has been difficult and been mainly electronic
- Ensure cardiac specialists are involved
  - Shouldn’t be giving thrombolytics to everyone and not everyone should be able to administer thrombolytic therapy

How has COVID-19 changed your code blue response?

- Limiting the number of people who are in the room
- Code cart and medication tray being kept outside the room
  - Pharmacist prepares the medication and transfers medication to a staff member that is inside the room

Has your opinion on the use of ACE-I/ARB in the ICU changed for COVID-19 patients?

- ACE2 enzyme has been shown to be a co-receptor for SARS-Cov2 viral entry
  - Concern that the use of ACE-I/ARB would increase the patient susceptibility to viral host entry
- Based on current evidence, these agents should be initiated or maintained in patients who have a primary indication for use
  - Heart failure, HTN, ACS
  - Primarily used in patients with cardiovascular disease
    - As long as there aren’t contraindications for using in the acute setting
- Peter’s opinion is unchanged compared to using to general use in critically ill patients
  - Pre-emptively withdrawing RASS inhibition should not be recommended
Has your use of NSAIDs changed due to COVID-19?
- The ACE2 mechanism as described above, was why the discussion on NSAID and COVID-19 started
  - The use of NSAID in other viral pneumonia has also been associated with worse outcomes
- In a cardiac ICU, they generally try to avoid all NSAIDs (other than ASA)
- Current evidence hasn’t found a link between NSAID use and COVID-19
  - Multiple reasons in a critically ill patient why we’d want to avoid NSAID use regardless

Have you found yourself using statins more than you may have otherwise?
- Statins have some anti-inflammatory effects
  - Can also increase IL-8 levels
- Not much evidence to suggest that statin use could be beneficial for COVID-19 patients
  - In patients with a primary indication for a statin, continue using
  - Wouldn’t initiate a patient on a statin just because they have COVID-19

How have you overcome some of the challenges that come from virtual rounding and not being physically present with the ICU team?
- It has certainly been frustrating and challenging at times
  - They’re critically ill requiring sedation, antimicrobials, and anticoagulation
    - Which can be difficult to remotely manage
- Not feasible to use video conferencing technology because there are multiple attendings/teams rounding in the same unit
- Things Peter has done to make interventions:
  - Keeping constant and consistent contact with residents, nurses, and on-site pharmacy staff
  - Paying attention to email with how quickly things are changing in terms of COVID-19 management
If you had to pass along some key points on COVID-19 and its management, what would those be?

- A lot of patients look and present very similar
  - Appropriate management of sedation, similar to severe ARDS
- Be patient, these aren’t typical ARDS or ICU patients, some require mechanical ventilation for >2 weeks
  - Pay attention to other potential infectious sources
- Keep delivering high quality critical care management as we’re used to doing
- Stay up to date on new literature via social media (Twitter)
- Be flexible